## REMARKS/ARGUMENTS

***Status of Claims***

Claims 57, 59, 61-65, 67-70, 101 and 112 are pending in the present application. In the Advisory Action mailed December 29, 2004, the Examiner indicated that the amendment mailed November 29, 2004 would be entered, but that the Declaration of David Zopf filed with the amendment would not be considered. The present response and RCE are filed to have the Zopf declaration considered. As noted in the previous response, the claims are now directed to methods in which at least 80% of the terminal galactose residues present on the glycoprotein are sialylated.

Claims 57, 59-65, 67-70, 101 and 112 remain rejected under 35 U.S.C. § 103(a) for allegedly being obvious over Bergh *et al.* (US Patent 5,272,066), Maras *et al.* (USP 5,834,251), Weinstein *et al.* (*J. Biol. Chem.*, 257:13845) and Williams *et al.* (*Glyconconjugate J.* 12:255). Claims 57, 59-65, 67-70, 101 and 112 are rejected under the doctrine of obviousness-type double patenting over claims in the parent patent (US Patent 6,399,363). Each of these rejections will be addressed in the order in which they were raised.

***Rejection under §103(a)***

The rejection of the claims over the cited prior art is respectfully traversed. As noted in the previously, the Examiner cites Bergh *et al.* and Maras *et al.* for teaching *in vitro* methods of enzymatic modification of glycoproteins using sialyltransferases, including ST3Gal III. The Examiner acknowledges, however, that neither reference teaches a commercial-scale method, nor does either reference discuss the extent of sialylation achieved in the methods. The Examiner cites Weinstein *et al.* for allegedly teaching conditions under which sialyltransferases can fully sialylate a substrate. Williams *et al.* is cited for allegedly teaching large scale recombinant expression of sialyltransferases.

As explained previously, the cited references fail to establish a proper *prima facie* case of obviousness of the claimed invention. In particular, the primary references fail to disclose *in vitro*, commercial-scale sialylation methods that achieve ***at least 80% sialylation*** of the target sites, as now claimed. The Examiner has not pointed to any specific teaching of large

scale production of modified glycoproteins in the cited art. In the Office Action, the Examiner stated that the suggestion to scale up the disclosed methods is implicit in the art. In the Advisory action, the Examiner points to Weinstein *et al.* for allegedly supporting the contention that one of skill would expect at least 80% sialylation in commercial scale methods. As noted previously, the reaction mixtures used in Weinstein *et al.* contained 60 µl (*see* Weinstein *et al.* page 13851). No evidence has been provided to show why one of skill would reasonably expect that similar rates of sialylation could be achieved at the commercial scale.

Applicants have previously provided evidence of the commercial success and long-felt but unsolved needs in the art (see, the First Zopf Declaration and Appendices 1-6 attached to the response mailed May 14, 2004). As noted previously, such evidence must be considered by the examiner in determining the issue of obviousness of claims for patentability under 35 U.S.C. §103 (MPEP §716.01(a)), assuming that a *prima facie* case of obviousness is maintained.

In the Final Office Action, although the Examiner acknowledged that the evidence of record shows commercial success of the invention, she raised certain issues with regard to the First Zopf Declaration. First, the impartiality of Dr. Zopf is questioned in that he is an employee of the assignee of the present invention. Second, she questions whether there is a nexus between the demonstrated success and the invention. In particular, the Examiner asserts that there is no evidence that commercial success is linked to specific limitations in the claims.

With regard to Dr. Zopf's impartiality, applicants note that the evidence provided to show success of the invention in this case has been generated by the assignee of the invention. Only the assignee has readily available information about the number of collaborations entered into to pursue this technology. In addition, Dr. Zopf has signed a declaration in which he states that all statements made there are true or believed to be true and acknowledges that willful false statements may jeopardize the validity of any patents issuing from the present application. In light of the above, applicants respectfully submit that the evidence of record should be considered.

The Examiner's concerns about the relationship between the commercial success and the claimed invention apparently question whether a proper nexus between the invention and

the commercial success has been established. According to M.P.E.P. § 716.03, "The term 'nexus' designates a factually and legally sufficient connection between the evidence of commercial success and the claimed invention so that the evidence is of probative value in the determination of nonobviousness. *Demaco Corp. v. F. Von Langsdorff Licensing Ltd.*, 851 F.2d 1387, 7 USPQ2d 1222 (Fed. Cir. 1988)."

To further clarify the nexus between the commercial success and the claimed invention, applicants have provided a second declaration from Dr. Zopf (the "Second Zopf Declaration"). Since the Declaration was not considered with the After Final response, Applicants respectfully request consideration of the Declaration with this response. As explained previously and stated by Dr. Zopf in Paragraph 4 of the Second Zopf Declaration, achieving and maintaining proper glycosylation is a major challenge in biotechnology manufacturing, and one that affects the industry's overall ability to maximize the clinical and commercial gains possible with these agents. Utilizing cell systems to produce recombinant glycoproteins requires balancing the cells' ability to produce the protein with their ability to attach the appropriate carbohydrates.

Exhibit 1 to the Second Zopf Declaration (Zopf and Vergis, *Pharmaceutical Visions*, pp10-14, Spring 2002) sets out some of the technical problems encountered in recombinant production of glycoproteins. As explained at page 11 of Zopf and Vergis, and illustrated in Figure 3, none of the currently used recombinant expression systems produce proteins having glycosylation as found in human cells (*see* Second Zopf Declaration Paragraph 5).

Dr. Zopf notes in Paragraph 6 of his Second Declaration that problems in glycosylation result in low yields of usable product, which contributes to the cost and complexity of producing these drugs. For example on page 11, Zopf and Vergis note that underglycosylation results in manufacturing losses of up to 80% of the product. Incorrect sialylation, in particular, affects the half-life of the drug, resulting in the need to administer higher and more frequent doses. This affects the cost of therapy, and potentially, the incidence of side effects. Thus, the ability to manufacture therapeutic glycoproteins with improved

glycosylation has been an important strategic goal of pharmaceutical and biotechnology companies.

The methods of the present invention are very effective in addressing this long felt need. There are at least two claim limitations that account for the success demonstrated in Dr. Zopf's First Declaration and Appendices 1-6. First, the claimed methods require that the step of contacting a glycoprotein with a sialyltransferase and other reactants occurs *in vitro*. The second relevant claim limitation is the requirement that the methods result in sialylation of at least 80% of the terminal galactose residues on the glycoprotein. In the opinion of Dr. Zopf, these two limitations (*in vitro* reaction and high degree of sialylation) are directly related to the success of the claimed process (*see* Second Zopf Declaration, Paragraph 7).

In Dr. Zopf's experience, producers of recombinant therapeutic proteins have been interested in the claimed *in vitro* methods because the methods can be used to improve glycosylation without altering the host cells or culture conditions that have been optimized for other purposes, such as yield. In addition, the methods can be used in combination with any expression system, such as bacteria, yeast, fungi, or plants. Prior to the advent of the claimed technology, producers of recombinant therapeutic glycoproteins had no commercially feasible means for achieving this goal.

The high degree of sialylation achieved using the methods of the invention is shown in the specification and the First Zopf Declaration. For example, Dr. Zopf states in paragraph 7 of his First Declaration that a consistent improvement in glycosylation was experienced when various companies used the claimed invention. The percentage of potential sites that lacked sialic acid as a terminal sugar, ranged from, 15% to 85%. After using the claimed invention, sialic acid occupied *greater than* 90% of possible sites. Figure 3 of the Zopf and Vergis paper provides further evidence in this regard.

These improvements have also been publicly noted by collaborators, thus demonstrating that improvements are generally recognized by those of skill in the art, not just by those at Neose (Second Zopf Declaration, Paragraph 9). For example, Exhibit 2 to the Second

Zopf Declaration is a copy of a presentation made by employees of Eli Lilly at the Biotechnology Industry Organization Meeting (BIO) held on June 26, 2001, in San Diego, California. As described therein, a "glycoprotein X" (GPX) was at sent by scientists at Eli Lilly to Neose for resialylation. The presenters conclude in the last slide of the presentation by noting that the methods restored sialic acid ***on 99% of exposed Gal residues and N-linked glycans***. These improvements, the Eli Lilly scientists concluded, resulted in slower plasma clearance and an increase in steady-state plasma concentration.

Exhibit 3 to the Second Zopf Declaration is a copy of Thomas *et al. Glycobiology* 14:883-93 (2004), which is the same as the manuscript provided as Appendix 1 to the response mailed May 18, 2004. This publication describes the results of research carried out by Neose scientists in collaboration with scientists from Avant Immunotherapeutics. As noted earlier, the glycosylation reactions described there (both sialylation and fucosylation) resulted in nearly all of the carbohydrates of the target protein terminating in the desired oligosaccharide structure (termed $sLe^x$). The proteins therefore had a ten-fold increase in affinity for the target receptor (termed E-selectin). The authors, including Avant Immunotherapeutics scientists, concluded that the *in vitro* glycosylation of the invention "***reduces heterogeneity of the glycan profile, improves pharmacokinetics and enhances carbohydrate mediated binding to E-selection.***" (*see* Abstract). Thus, both Avant Immunotherapuetics and the reviewers of this manuscript felt that the observed improvements in binding of the modified protein was commercially valuable and worthy of publication in a respected scientific journal.

Based on the above, Dr. Zopf concludes in Paragraph 12 that the claimed methods have been extremely effective in restoring a high degree of sialylation. Indeed, the degree of sialylation achieved is routinely well over 80%. This has resulted in improved biological function. Moreover, the improved results are publicly noted by collaborators and are accepted by third party reviewers at respected journals. According to Dr. Zopf, These results coupled with the fact that potential partners need not modify existing culture conditions have been directly responsible for the commercial success of the claimed invention.

As noted in his First Declaration, Dr. Zopf has directly negotiated use agreements of the claimed technology with over 20 companies to assess the feasibility of the technology for *in vitro* sialylation of recombinant therapeutic glycoproteins in development. All feasibility studies referred to in his declaration have been successful. As set forth in his declaration, many of these successful feasibility studies have led to ongoing negotiations for commercial licenses to the technology for large-scale manufacture of human glycoprotein therapeutics. In addition, the present technology is being employed as an essential part of ongoing collaborative research and development agreements with other companies to develop commercial manufacturing methods for cancer vaccines and treatments for neurological diseases.

In view of the foregoing, it is evident that the present invention satisfies a long-felt need for providing methods for *in vitro* sialylation of saccharide groups present on recombinantly produced glycoproteins. Prior to the advent of the present invention, a long-felt need existed for an *in vitro* procedure to enzymatically cap carbohydrate chains that lacked a terminal sialic acid. The present invention satisfies this need.

All of the above evidence also supports Dr. Zopf's opinion that the commercial success of the present invention is directly related to the innovative process and thus, a nexus between the claimed invention and commercial success has been established. In particular, it shows that the process has found success in the market place because it is carried out *in vitro*. This provides the flexibility needed to adapt the glycosylation process to existing expression systems. In addition, the demonstrated high rates of glycosylation are now specifically claimed.

Finally, the commercial success demonstrated above is directly derived from the invention claimed, in a marketplace where the consumer is free to choose on the basis of objective principles. The collaborations described above are the result of arms length negotiation between sophisticated parties. The demonstrated success such success is not the result of heavy promotion or advertising or other business events extraneous to the merits of the claimed invention. Thus, applicants respectfully submit that the Zopf Declarations and Appendices 1-6 establish a nexus between the claimed invention and evidence of commercial success.

As such, the foregoing secondary indicia represents objective evidence sufficient to rebut a *prima facie* case of obviousness. Accordingly, the Examiner is respectfully requested to withdraw the 35 U.S.C. §103(a) rejection and send this application to issue.

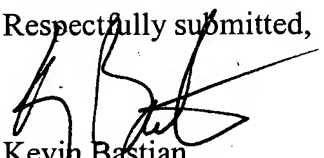
***Obviousness-type Double Patent Rejection***

In response to the obviousness-type double patenting rejection over claims in the parent patent (US Patent 6,399,363), Applicants will file an appropriate terminal disclaimer, once the outstanding rejection under §103(a) is resolved.

## CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at 415-576-0200.

Respectfully submitted,



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